REMARKS

The present Amendment is in response to the Examiner's Office Action mailed February 27, 2001. Claims 1-9, 14, 18-24 remain in this application. Claims 10-13, 15-17 and 25-35 have been canceled. Claims 36-45 are new. Reconsideration of the application is respectfully requested in view of the above amendments to the claims and the following remarks. For the Examiner's convenience and reference, Applicants' remarks are presented in the order in which the corresponding issues were raised in the Office Action.

1. Objection to Claim 14

The Examiner objects to claim 14 as being improper dependent form for failing to further limit the subject matter of a previous claim. Applicants amend claim 14 to dependent on claim 1. Withdrawal of this ground of objection is respectfully requested in view of the amendment.

2. Rejection under 35 U.S.C. § 101

The Examiner rejects claims 1-24 under 35 U.S.C. § 101 on the ground that the claimed invention is not supported by either a specific and/or substantial asserted utility or a well-established utility. Specifically, the Examiner states that "[t]he claimed method for selecting tester proteins capable of binding to a target peptide or protein, is not supported by a specific asserted utility and does not, without further research and experimentation, provide an immediate benefit to the public". Applicants respectfully traverse the Examiner's grounds for utility rejection as being improper and unsupported.

Under the "Revised Interim Utility Guidelines" of the PTO, if at least one specific, credible, and substantial utility is provided, a rejection under 35 U.S.C. § 101 should not be made.

1) Specific Utility Provided

The claimed invention provides an efficient method for high throughput screening of a diverse protein library against a specific target protein. Classes and highly specific examples of target proteins including epidermal growth factors (EGFs), transferrin, insulin-like growth factor, transforming growth factors (TGFs), interleukin-1, and interleukin-2 are provided in the Specification (See pp. 44-48, "The Target Proteins and Peptides"). Each target protein listed

can be used in the claimed method for screening against the protein library. It is taught that the protein library may be a single-chain antibody, scFv which typical comprises a V_H domain and a V_L domain in polypeptide linkage. The proteins screened according to the method can be used in diagnostic applications for the target protein and as therapeutics for a specific disease associated with the target protein.

As taught in the Specification, antibodies identified through the method against a cell surface protein or receptor such as platelet glycoprotein IIb/IIIa receptor can be used to treat coronary artery disease. Antibodies identified through the method against CD4, CAMPATH-1 can be used to treat autoimmune diseases. See Specification, page 45, last paragraph. The myriad of specific utilities provided by the method of the present invention is endless.

To further demonstrate that a specific asserted utility has been provided, the Examiner's attention is drawn to original dependent claims 21-23 which recite specific disease associated proteins as target proteins. As can be seen from the originally claimed method, at least one specific utility has clearly been provided.

2) Substantial Utility Provided

A "substantial utility" is defined by the PTO Training Materials for the "Revised Interim Utility Guidelines" as a "real world" use. An assay method for identifying compounds that themselves have a "substantial utility" is considered to be a "real world" use.

As discussed above, the claimed method provides a high throughput assay for screening proteins such as therapeutic antibodies that can bind to specific disease-associated proteins. The resulting screened proteins can be used in diagnostic applications and for treating specific diseases in the clinic. Applicants therefore submit that a "real world" use demonstrating a substantial utility has also been provided.

3) Credible Utility Provided

The claimed method also has credible utility. It is well known that antibodies are widely used for the diagnosis and treatment of disease, the most celebrated one being HERCEPTIN® (Genentech Inc.) which has been shown to have substantial utility in treating breast cancer. Many commercial entities such as Cambridge Antibody Therapeutics use various screening methods such as phage display to select for therapeutic antibodies. The claimed high throughput assay for screening compounds such as therapeutic antibodies that can bind to specific disease associated proteins would be readily recognized to have credible utility as an

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alternative to phage display and other such screening methods for selecting therapeutic antibodies. Applicants therefore submit that a credible utility has also been provided.

In view of the specific, credible, and substantial utility of the claimed method, the pending utility rejection should be withdrawn.

3. Rejections under 35 U.S.C. § 112, First Paragraph

The Examiner rejects claims 1-24 under 35 U.S.C. § 112, First Paragraph for insufficient written description and lack of enablement. The grounds for the Examiner's rejection are based on the rejection under 35 U.S.C. § 101. Specifically, the Examiner states that "since the claimed invention is not supported by either a specific and/or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention".

As discussed in Section 2 above, the Examiner's rejection under 35 U.S.C. § 101 is improper and unsupported and should be withdrawn. Given that the pending utility rejection is unsupported, the utility rejection cannot support the pending rejection under 35 U.S.C. § 112, First Paragraph. For this reason, Applicants respectfully request that the rejection under 35 U.S.C. § 112, First Paragraph be withdrawn.

4. Rejections under 35 U.S.C. § 112, Second Paragraph

The Examiner rejects claims 2-4, 10-16, and 18 under 35 U.S.C. § 112, Second Paragraph for being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicants address each of the indefiniteness rejections in detail below.

1) Claims 2 and 4: "a first transcription sequence encoding" etc.

Claims 2 and 4 are rejected as being indefinite on the grounds that it is not clear that there is a difference between the terms "a first transcription sequence encoding etc." and "a first nucleotide sequence encoding etc."

Claims 2 and 4 are amended to specify "a first transcription sequence encoding either the activation domain or the DNA binding domain of the transcription activator, and a sequence encoding one of the tester proteins". In view of the amendments to these claims, the difference between the two specified sequences would be well understood to one of ordinary skill.

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Withdrawal of the rejection under 35 U.S.C. § 112, Second Paragraph in regard to claims 2 and 4 is therefore respectfully requested.

2) Claim 3: "the target fusion protein" etc.

Claim 3 is rejected as being indefinite on the grounds that the terms a "target fusion protein" and a "target sequence encoding the target protein or peptide" do not have equivalent meaning but appear to be used as equivalent terms in the claim.

Independent claim 1 as amended specifies a target fusion protein comprising "either the DNA binding domain or the activation domain of the transcription activator which is not comprised in the tester fusion proteins, and a target peptide or protein." Claim 3 specifies sequences encoding these components of the target fusion protein. In view of the amendments to these claims, claim 3 would be well understood to one of ordinary skill. Withdrawal of the rejection under 35 U.S.C. § 112, Second Paragraph in regard to claim 3 is therefore respectfully requested.

3) Claim 4: "the target fusion protein" etc.

Claim 4 is rejected as being indefinite on the grounds that the terms a "target fusion protein" and a "target sequence encoding the target protein or peptide" do not have equivalent meaning but appear to be used as equivalent terms in the claim.

In view of the amendment to claim 4, the difference between the two specified sequences would be well understood to one of ordinary skill. Withdrawal of the rejection under 35 U.S.C. § 112, Second Paragraph in regard to claim 4 is therefore respectfully requested.

4) Claims 10-13

The Examiner's rejection of claims 10-13 under 35 U.S.C. § 112, Second Paragraph is moot in view of Applicants' cancellation of these claims.

5) Claim 14

Claim 14 is rejected under 35 U.S.C. § 112, Second Paragraph for lacking antecedent basis for the claim language "first nucleotide sequence" and "the second nucleotide sequence". Applicants amend claim 14 to replace the terms "first nucleotide sequence" and "the second

nucleotide sequence" with the terms "polypeptide subunit" and "the second polypeptide subunit", respectively, and to render claim 14 dependent on claim 1 in order to provide sufficient antecedent basis for these two terms as amended. Withdrawal of the rejection under 35 U.S.C. § 112, Second Paragraph is respectfully requested.

6) Claims 15 and 16

The Examiner's rejection of claims 15-16 under 35 U.S.C. § 112, Second Paragraph is moot in view of Applicants' cancellation of these claims.

7) Claim 18

Claim 18 is rejected under 35 U.S.C. § 112, Second Paragraph on the grounds that the terms "the selected clones", "the first and second nucleotide sequences" and the "isolated tester expression vectors" lack antecedent basis.

Applicants amend dependent claim 18 to render it an independent claim by incorporating the limitations of claim 1 from which claim 18 is originally dependent. Applicants submit that claim 18 is sufficiently definite and well understood by one of ordinary skill in the art. Withdrawal of the rejection under 35 U.S.C. § 112, Second Paragraph is therefore respectfully requested.

5. Rejection under 35 U.S.C. § 102

Claims 1-4, 10-17, 20, 21, and 24 are rejected under 35 U.S.C. § 102(a) in view of Hoeffler and Russell (1999, WO 99/28502). Specifically, the Examiner states that this reference is a method of screening a DNA construct library encoding single chain fragments of immunoglobulin variable domains (sFv). Yeast expression vectors that are constructed in vitro via a series of subcloning steps (e.g., bacterial vectors) are used in the screening. Claim 1, page 111.

Independent claim 1, as amended, specifies a method for screening a highly diverse library of tester proteins each having two variable domains. The diversity of the tester proteins in the library is specified to be at least $1x10^7$. Support for the claim language appears at the Specification at page 28, line 28.

In contrast, the sFv library constructed by Hoeffler and Russell has a diversity of $3.6X10^6$. Page 54, lines 5-6. Hoeffler and Russell teaches that this level of diversity of the

library is sufficient and was verified by fingerprinting amplified clones. Page 54, lines 5-7. Given that Hoeffler and Russell fails to teach a screening method employing the level of diversity specified in independent claim 1, the cited reference fails to anticipate the claimed invention. Withdrawal of the rejection under 35 U.S.C. § 102(a) is therefore respectively requested.

6. Obviousness Rejections under 35 U.S.C. § 103

The Examiner rejects claims 1-12, 20, and 24 under 35 U.S.C. § 103(a) as being unpatentable in view of Nandabalan et al. (US Patent No: 6,057,101), and Hoeffler and Russell. Specifically, the Examiner states that the Nandabalan reference teaches methods for detecting protein-protein interactions that include expressing a library of tester fusion proteins and target fusion protein in yeast cells. The Examiner further states that

> [t]he Nandabalan reference also teaches the diversity of fusion proteins is at least $1x10^6$, $1x10^{10}$, and $1x10^{12}$ in claims 38-42. If the diversity of each of the **two libraries** is at least 50,000, the **total diversity** is at least $2.5x10^9$.

The Office Action (Paper No: 6) at page 15, lines 13-15, emphasis added,

The diversity of the tester proteins within the library in present invention is not equivalent to the "total diversity" according to the Examiner's interpretation of the Nandabalan reference. As clarified in claim 1 and 7-9, the claimed diversity relates to the diversity of the tester proteins which is achieved by the variability of the first polypeptide subunit (e.g., an antibody V_H) and the second polypeptide subunit (e.g., an antibody V_L) within the library.

By contrast, the **total diversity** calculated by the Examiner is a result of the combination of two separate Nandabalan libraries: the tester protein library and the target protein library. Thus, Nandabalan fails to teach a single library of tester proteins having a diversity of at least $1x10^7$ as specified in the pending claim 1 of the present invention.

As discussed in Section 6 above, the secondary reference cited by the Examiner, Hoeffler and Russell, does not teach the at least $1x10^7$ level of diversity specified in the claims and missing in Nandabalan et al. Since none of the cited references teach the level of diversity specified in claim 1, these references are insufficient to render claim 1 and the claims depending therefrom obviousness under 35 U.S.C. § 103(a).

Applicants further note that neither Nandabalan et al. nor Hoeffler and Russell motivate one to employ the level of diversity that is being claimed. Instead, Hoeffler and Russell teaches away from the present invention by stating that "[t]he diversity of the library doesn't need to be

much above 10^6 since the transformation capacity of yeast is generally 10^7 or below". In view of this teaching away by Hoeffler and Russell, one of ordinary skill in the pertinent art would not look to modify Nandabalan et al. in view of Hoeffler and Russell and arrive at the claimed invention. Furthermore, these references fail to teach or suggest how to achieve the high level of diversity achieved by the present invention. For these further reasons, Applicants submit that independent claim 1 is not rendered obvious by Nandabalan et al. in view of Hoeffler and Russell under 35 U.S.C. § 103(a). Withdrawal of this ground of rejection with regard to claims 1-12, 20, and 24 is therefore respectfully requested.

CONCLUSION

In light of the remarks and arguments set forth above, Applicants earnestly believe that are entitled to a letters patent, and respectfully solicit the Examiner to expedite prosecution of this patent application to issuance. Should the Examiner have any questions, the Examiner is encouraged to telephone the undersigned.

Respectfully submitted,

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